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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MAURICE MOLONEY, JOENEL ALCANTARA,
and GIJS VAN ROOIJEN

Appeal 2008-3488
Application 09/402,488
Technology Center 1600

Oral Hearing Held: August 12, 2008

Before DEMETRA J. MILLS, ERIC B. GRIMES, and
FRANCISCO C. PRATS, *Administrative Patent Judges.*

ON BEHALF OF THE APPELLANT:

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P R O C E E D I N G S

MS. BOBO-ALLEN: Calendar Number 9, Appeal Number 2008-3488. Ms. Brinckerhoff.

JUDGE MILLS: Thank you. As a preliminary matter, I would like you to take a minute and say and spell your name for the court reporter and also introduce your colleague.

MS. BRINCKERHOFF: Okay. I'm Courtenay Brinckerhoff, C O U R T E N A Y B R I N --

Court Reporter: B R I N --

MS. BRINCKERHOFF: -- C K E R H O F F. And, my colleague is Rachel Pilloff, R A C H E L P I L L O F F.

Court Reporter: -- O F F?

MS. BRINCKERHOFF: Yeah.

JUDGE MILLS: Okay, and you have 20 minutes and you may begin when you're ready.

MS. BRINCKERHOFF: Thank you. There are two categories of rejections that we're appealing today, the enablement rejection and the obviousness rejections. I would like to discuss the enablement first, although I also plan to discuss obviousness.

The present invention is constructed to a method of preparing a combinant polypeptide, and the method involves creating a fusion protein with a chymosin propeptide and the peptide of interest. And, in cleaving that fusion protein with an auto catalytically maturing
-- to just chymosin and pepsin.

Claim 51 recites that the host cell is bacterial in -- and is argued separately in the Briefs for the 112 rejection. As reflected in Page 1 of the specification, the invention provides an improved method of recovering a

recombinant polypeptide and provides a method for efficient and accurate cleavage of the fusion protein.

Although the invention is directed to an improvement in recombinant protein production, much of the enablement rejection questions enablement of recombinant protein production per se. But, Applicants have submitted evidence to show that recombinant protein production in a wide variety of -- was well enabled as of the filing date. For example, the Meade Patent 5,827,698 was directed to the production of amino globulin in the milk -- animal, and this involved the expression and assembly of heavy and light chains. Also, the Butler 1997 article reported the production of human fibrinogen in the milk of mice, sheep, and pigs, and this involved the expression and assembly of three chains of fibrinogen molecule.

The Janne 1992 article reports on the use of transgenic animals as bioproducers of pharmaceutical proteins as set forth at Page 275 from Janne. By September of 1991 three reports were published representing a real breakthrough in the field and demonstrating feasibility of farms animals as bio-producers of pharmaceuticals. Janne summarizes these developments and in its conclusion on Page 278 states that although the production of transgenic bioreactors is still in its infancy and we eagerly await commercial application, the approach certainly is viable.

With regard to plants, Applicant submitted references such as Hiatt 1990, which was ten years before our filing date, and the Hiatt Patent which show the production of antibodies in transgenic plants. And, again this involves the expression and assembly of heavy and light chain.

JUDGE GRIMES: On a basic level, there's nothing really different about your method here compared to other methods of producing recombinant fusion proteins except for the chymosin and the use of the particular proteins. Isn't that correct?

MS. BRINCKERHOFF: Exactly. So -- I'm sorry, Lyons 1996 with regard to production in plants says that -- I'm sorry Lyons was 1996 -- that there is ample evidence that transgenic plants are a feasible alternative system to the production of recombinant protein pharmaceuticals.

So, these references and the other references Applicant submitted show that recombinant protein production was well enabled. The Examiner cited references alleged to undermine enablement, but the references that the Examiner recites really address issues that arose as recombinant protein production moved from the laboratory into the marketplace, such issues pertinent to commercialization like efficiency and cost effectiveness.

Also, some of the references recited by the Examiner relate to issues with gene therapy of the production of
knock-out means, but the issues discussed in those articles are not really pertinent when the goal is recombinant protein production itself.

Our Briefs go through each of the references recited by the Examiner, so unless there are any specific questions we would ask the Board to refer to our Briefs and the references themselves on these issues.

JUDGE MILLS: I had a general question. In the final rejection, the Examiner only brought up with regard to the enablement rejection three references and it looks like he added several of them in the answer. Can --

would you like to speak to that or -- it looks like you address them all in the Reply Brief and in the brief.

MS. BRINCKERHOFF: We did. He -- we looked at the MPEP and weren't sure if it was, if it was proper for him to cite new references in the Examiner's answer. Also, this application has been pending since 2000, so we really wanted to just move forward instead of trying to reopen prosecution. We do address each of the new references in our Reply Brief and these are references that either are several years before our priority date or are after our priority date and talk about issues commercialization for gene therapy. So I think even -- even looking at these references, I think the record as a whole supports enablement.

JUDGE MILLS: I don't have any further questions about enablement. You can move onto the obviousness rejection.

MS. BRINCKERHOFF: The main obviousness rejection is based on a combination of Ward, Walsh and Yonezawa, and looking at these references they do not suggest a method of producing a peptide that involves making a fusion peptide with a chymosin propeptide sequence and then cleaving that with an aspartic protease.

Ward is directed to fusion protein with optional linkers and is cited for teaching the pro-sequence of bovine chymosin and a list of possible linkers, but Ward does not give any guidance on how to cleave the linker except for its general statement that endoprotinases or chemical agents can be used to cleave its fusion proteins.

Also, while not raised in our briefs, I noticed while preparing for this hearing that Ward uses the term prochymosin sequence to refer to the entire

sequence of the chymosin precursor including the propeptide and the mature chymosin sequence, and this is seen at Columns 1 and 2 of Ward when it discusses its previous work to express chymosin. So under this construction of Ward, that would not be within the scope of the claims because our claims require that the propeptide sequence be directly linked to the peptide of interest.

Turning now to Walsh, Walsh teaches the use of a linker based on the bovine -- sequence that is cleaved by chymosin. Walsh created two linkers from residues 101 to 107 or 97 to 113 of Bovine -- and found that they were cleaved by chymosin at the femat junction between residues 105 and 106. Walsh found that the longer link worked better and that cleavage depended on the extended region around the cleavage site. Yet Yodazawa studied different phlormetric substrates that it would use to access -- activity, and is cited because it also has fee residue at the P1 position in some of its, in some of its substrate and found that that had a -- effect on the hydrolysis rate.

Looking at these references as a whole does not suggest the present invention. Importantly, there is no expectation of success that you could use in aspartic protease to cleave the chymosin propeptide from the peptide of interest -- based on expectation of success on Walsh's report of cleavage at a femat linkage and the fact that the chymosin propeptide sequence ends with a fee residue. And, also his belief that met or methionine would usually be the first amino acid of a peptide and this rationale is set forth in at Pages 10 to 11 of the December 30, 2005, Office Action.

In response to this, Applicant submitted a Rule 132 Declaration of Inventor, Dr. Moloney, that explains that the Examiner's basis for

expectation of success was not scientifically sound. First, the declaration shows that chymosin does not -- junction. The cleavage of chymosin depends on an extended region of surrounded sequences. For example, for the case -- linkers studied by Walsh it is believed that a specific floor residue sequence of ser-b-met-ala (phonetic sp.) is believed to be essential for cleavage by chymosin, and this is shown in the Visser and Shattenkerk articles submitted with the Rule 132 Declaration.

The present invention does not rely on those residues and in fact in the examples in the specifications do not have those residues around the cleavage point. Example 1 has cleavage at Phe-Val linkage and Example 2 has cleavage at Phe-Ser linkage.

The Declaration also explains that methionine is not necessarily going to be a first residue of the polypeptide. While methionine is usually the start codon, the mature peptide of interest may not start with methionine. And, this again is reflected in our examples. For Example 1 the first residue of the peptide of interest was Val, or Valine, and for Example 2 the first residue was Ser, or Serine. So the Rule 132 Declaration shows that the cited references do not have any expectation of success for the present invention.

We also emphasize that this is not a situation as contemplated in KSR where there was a limited number of predictable solutions. There's almost an infinite number of options for a link for peptide and a wide variety of cleavage agents that could be used to cleave from, and there's no apriori predictability that a given cleavage agent like aspartic protease would be able to accurately and reliably cleave a protein to the desired site.

JUDGE MILLS: Don't we have a clear teaching in Ward however, that they use a cleavable linker which can be the pro-sequence of chymosin and that it's inherently cleaved? Wouldn't people with skill in the art know it's inherently cleaved? Maybe not where it's inherently, where it's being cleaved, but they know it's a cleavable linker.

MS. BRINCKERHOFF: But there's, there's no teaching in Ward of to cleave that with an aspartic protease, and Ward actually lists as a separate category linkers that are cleaved by chymosin and those linkers wouldn't include the bovine casein sequence of Walsh which the prior art had really used that casein sequence as something to be cleaved by chymosin.

JUDGE MILLS: I'm not sure I understand your argument with respect to Walsh -- I mean Ward not teaching cleaving the linker. I mean, they're obviously providing a cleavable polypeptide because they want it cleaved.

MS. BRINCKERHOFF: In, in some embodiments, yes, but our claims recite that the, the fusion protein is cleaved by an aspartic protease, and Ward does not teach that you should cleave the pro-sequence of bovine chymosin within an aspartic protease. There's no teaching of how to cleave that, to cleave that embodiment. And, throughout prosecution the Examiner never asserted that, that Ward provided any teaching on how you would cleave it.

At Column 8 it, it also does mention that cleavage of the fusion protein is useful, is not necessary. And at Column 14, about the middle of the column, the only teaching is that the cleavable linker may be cleaved using techniques known in the art to release the desired polypeptide. And,

then the next paragraph, in some embodiment cleavage by chemicals or endoproteinthesis could be effective.

JUDGE MILLS: Why isn't Walsh a teaching of a technique known in the art of cleaving a cleavable linker with --

MS. BRINCKERHOFF: Well, the claims aren't directed to a linker and cleaving a cleavable linker. The claims are directed to a chymosin propeptide that is cleaved by aspartic protease, and in Walsh the linker that is cleaved is not a chymosin propeptide. It's, it's a different protein. It's a sequence based on a different protein, a casein protein. So while Walsh does show that chymosin can be used to cleave a protein, it does not show that chymosin can be used to cleave our fusion protein. And, the studies surrounding Walsh where the extended sequence around the cleavage site were important show that just knowing that chymosin can cleave one peptide doesn't predict or give a basis for predicting that chymosin could cleave a different fusion protein with different sequences on the cleavage site.

So the Walsh, the Walsh linker is an entirely different protein and it's a milk protein. So, chymosin in, in -- so I guess chymosin in nature is involved in cleavage of milk protein clotting factor. I think that's what casein is referred to.

So the Walsh is based on the natural amino activity of chymosin that cleaves its milk protein, so it uses its milk protein as a linker. So it's really doesn't give any reason to expect that chymosin would be able to cleave the chymosin propeptide from a, a peptide of interest.

JUDGE MILLS: What about Yonezawa?

MS. BRINCKERHOFF: Well, again Yonezawa -- the substrates of Yonezawa have nothing to do with the chymosin part, the chymosin propeptide sequence. There's no, there's nothing in Yonezawa that you could extrapolate or generalize to cleavage of the fusion protein that's recited in the present claim. The only thing that's common between Walsh and Yonezawa and even Dunn is having a fee residue at the cleavage site. But, Walsh and Yonezawa and Dunn and Visser and Shattenkerk all show that that sequence alone is not, is not what is driving or permitting cleavage. And, each of the substrate study residues upstream and downstream of the cleavage site were important to the cleavage reaction.

Just because I just touched on it, the Dunn reference that was recited in one of the other obviousness rejections of the Dependent Claims was cited because it shows cleavage by a different aspartic protease such as pepsin or human cathepsin-D. But, the substrate use, the protein that was cleaved was based on a substrate of porcine pepsin. And, again the only similarity between that substrate and our claimed fusion protein is the fee residue at the cleavage site. There's no other sequence similarity between the Dunn substrate and our chymosin propeptide sequence.

And, again all of their references cited in this context show that it's not having the fee residue there that drives the cleavage. The extended sequences up and down the stream of the cleavage site are important. Did you have any other questions?

JUDGE MILLS: I don't have any further questions, no.

MS. BRINCKERHOFF: For, for these reasons and for the reasons in the Brief, we believe that the obviousness rejections are improper and should

be reversed and, as stated previously, that the enablement rejections are improper and should be reversed. Thank you.

JUDGE MILLS: Okay, thank you.

JUDGE GRIMES: Thank you.

(Whereupon, the hearing concluded on August 12, 2008.